

Antiviral Drugs

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- **Learning Objectives**

1. **Classify antiviral drugs based upon their site of inhibition in the viral replication cycle.**
3. **Explain their mechanism/s of action.**
4. **Describe their major therapeutic indications.**
5. **Compare their pharmacokinetic properties.**
6. **Recognize their adverse side effects and potential for drug interactions.**
7. **Define the factors that regulate antiviral drug resistance.**

Drug List:

Amantadine, Rimantadine, Zanamavir, Oseltamivir.

Idoxuridine, Trifluridine

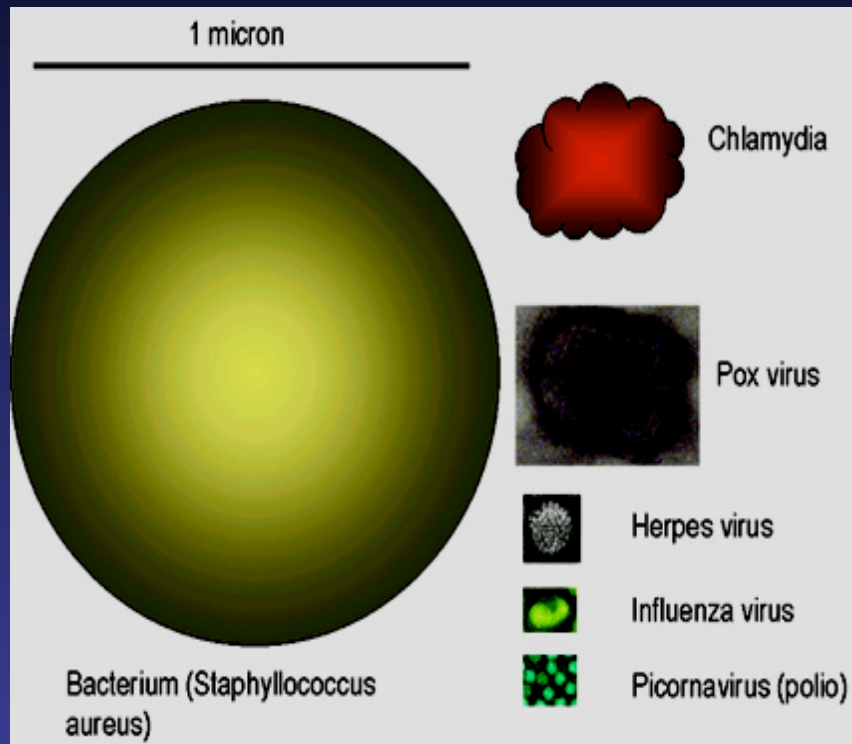
Acyclovir, Valacyclovir, Ganciclovir, Valganciclovir.

Foscarnet, Ribavirin.

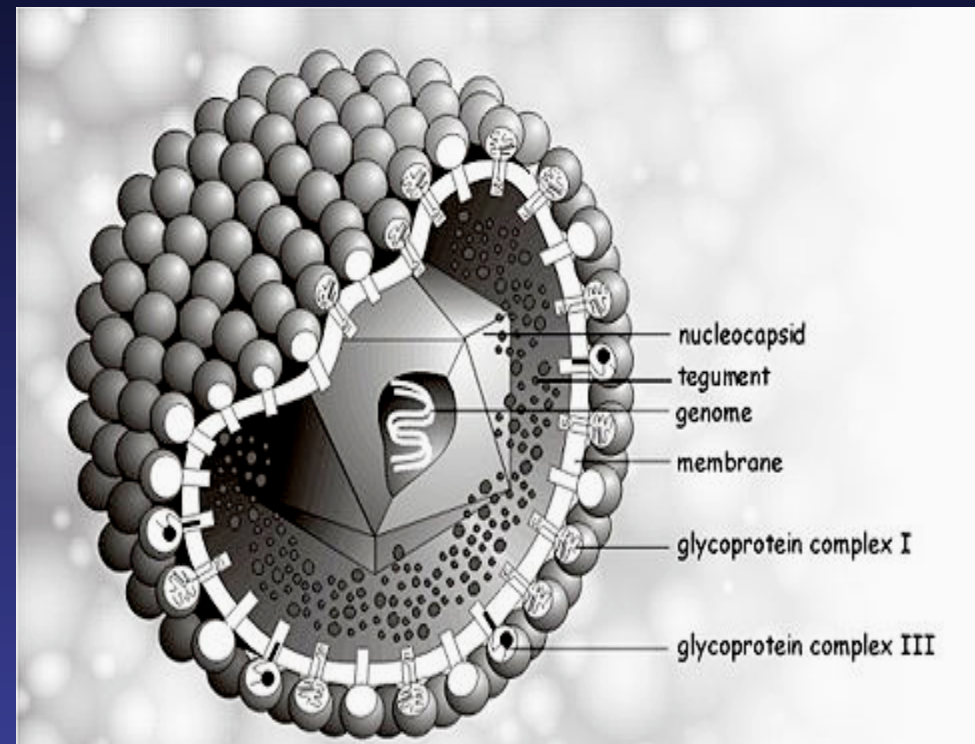
Interferon α -2b

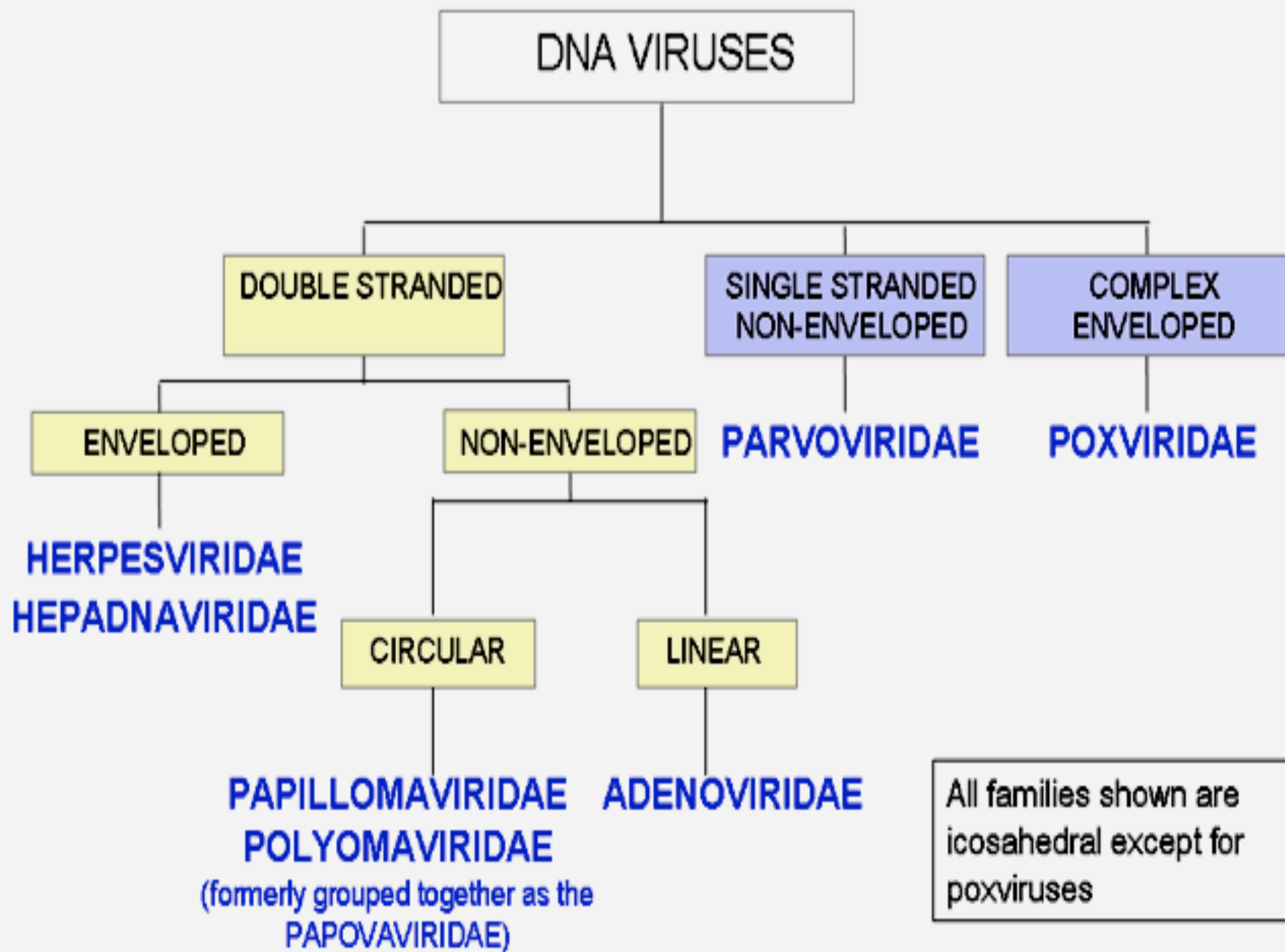
Viruses: Obligate Intracellular Parasites

- They come in all sizes.



-- General Structure is similar.





RNA VIRUSES

SINGLE STRANDED positive sense

ENVELOPED

ICOSAHERAL

FLAVIVIRIDAE
TOGAVIRIDAE
RETROVIRIDAE

HELICAL

CORONAVIRIDAE

NONENVELOPED

ICOSAHERAL

PICORNAVIRIDAE
CALICIVIRIDAE

SINGLE STRANDED negative sense

ENVELOPED

HELICAL

ORTHOMYXOVIRIDAE
PARAMYXOVIRIDAE
RHABDOVIRIDAE
FILOVIRIDAE
BUNYAVIRIDAE
ARENAVIRIDAE

DOUBLE STRANDED

NONENVELOPED

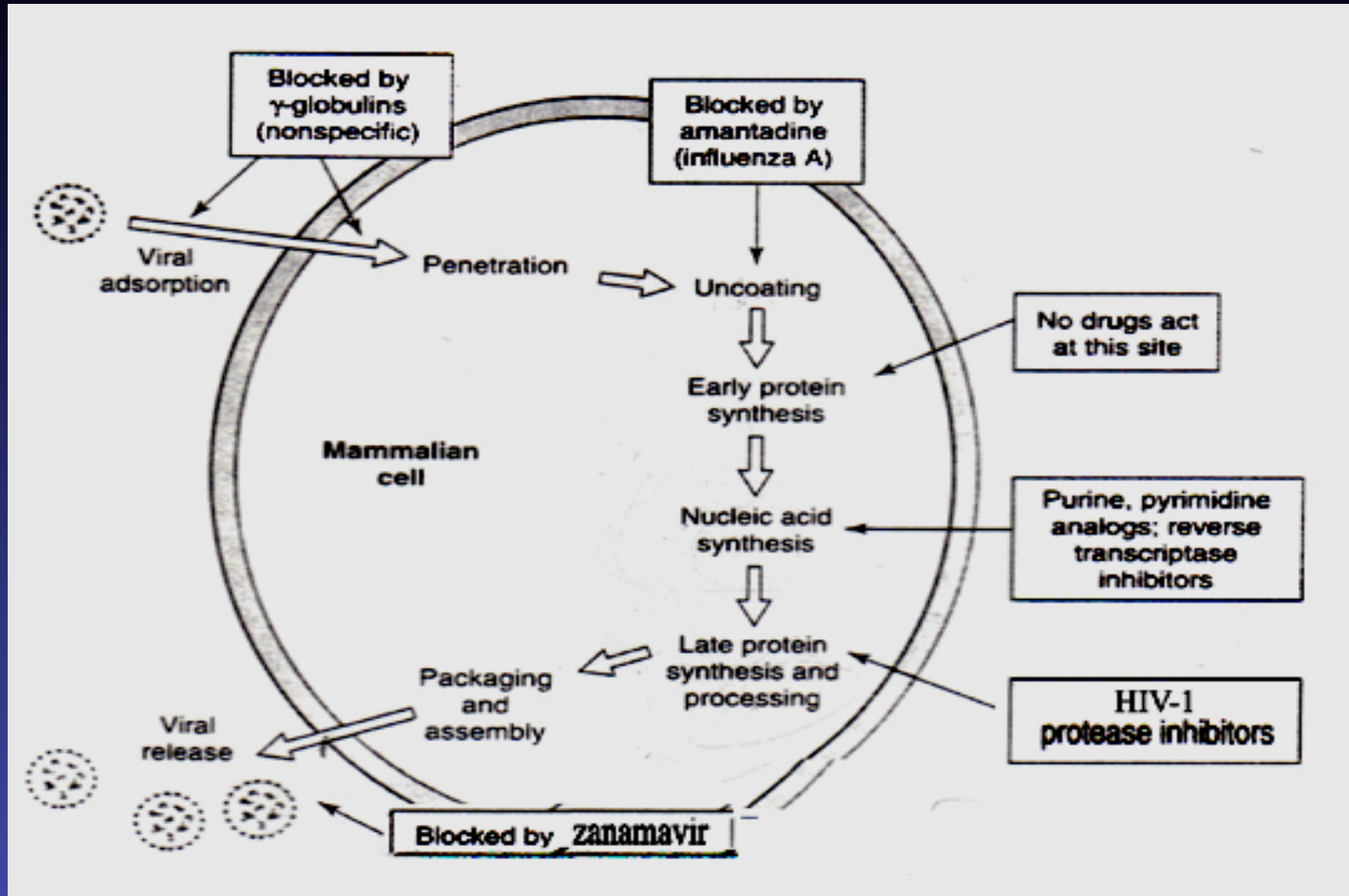
ICOSAHERAL

REOVIRIDAE

Viral Replication: General Scheme

- Adsorption to and penetration of susceptible cells
- Synthesis of early, nonstructural proteins
- Synthesis of RNA or DNA
- Synthesis of late, structural proteins
- Assembly of viral particles and their release from cell

Viral replication cycle: General Scheme



Difficulties in Generating Effective Antiviral Drugs.

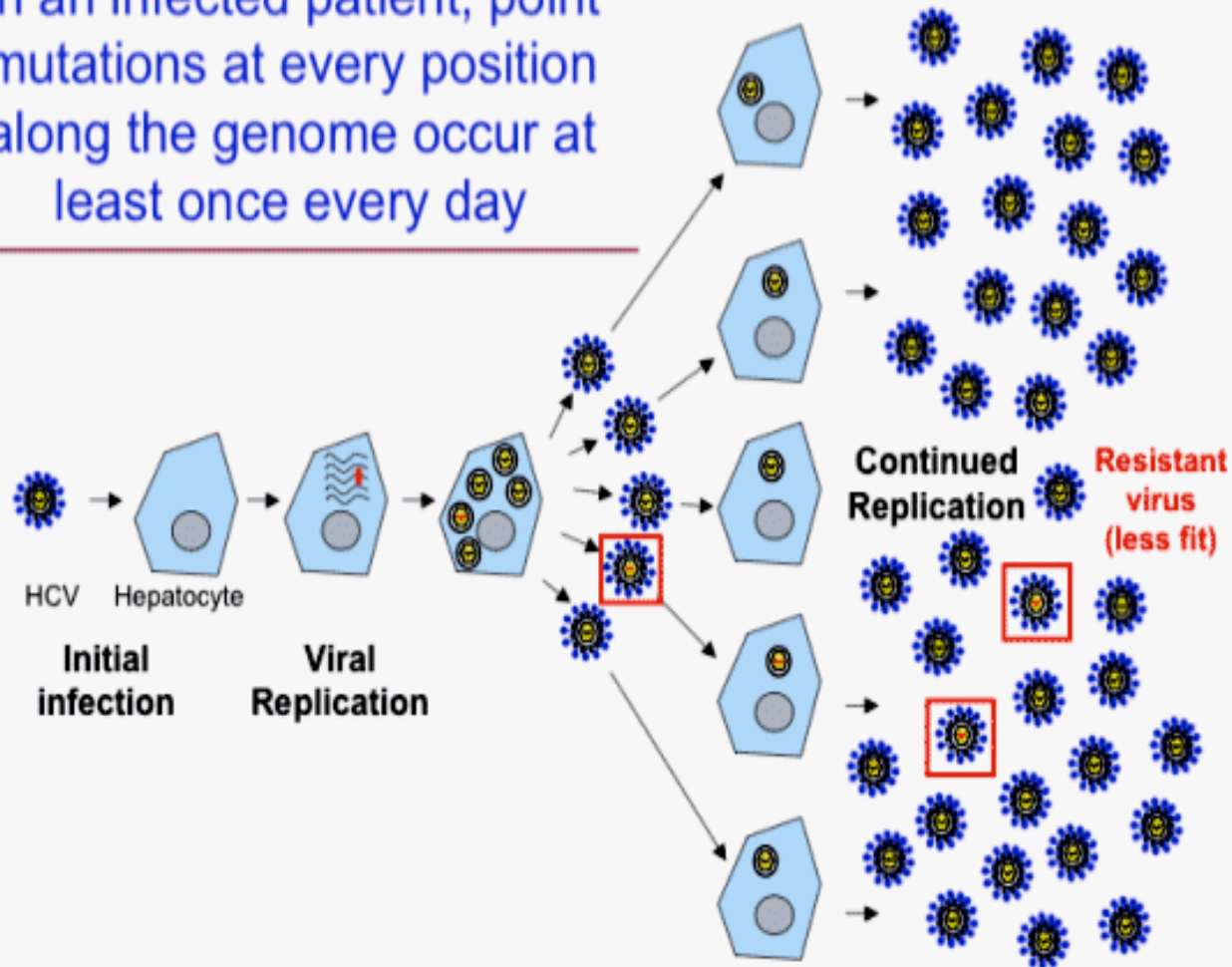
- ❑ **Lack of specific viral targets.**
- ❑ **Viruses replicate intracellularly.**
- ❑ **Asymptomatic during rapid growth phase.**

- **Escape from Immune Surveillance.**
- **Persistence of Latent Reservoirs.**
- **Generation of Drug Resistance.**

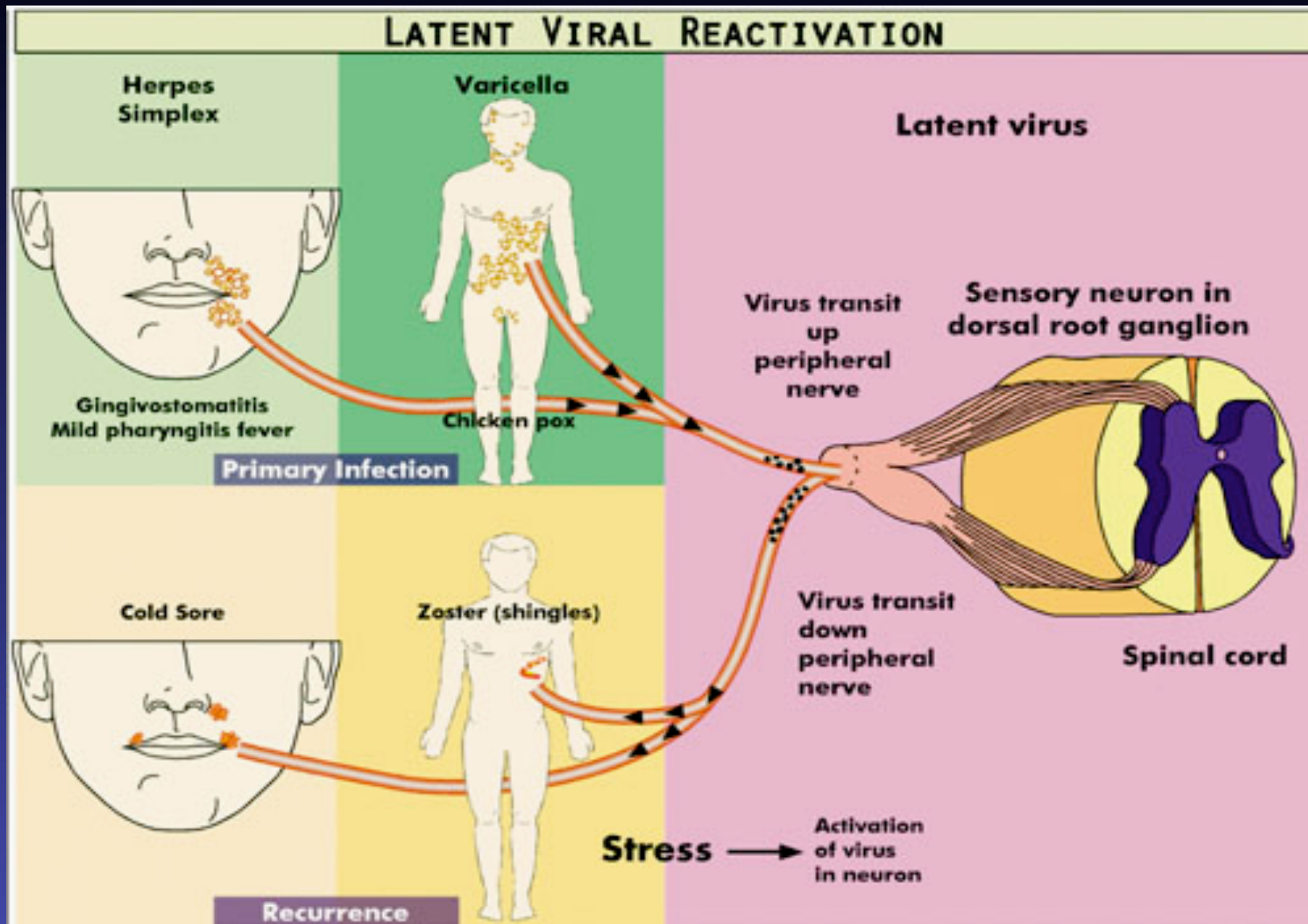
**** Acyclovir was the first anti-viral drug to specifically target viral enzymes.**

Escape from Immune Surveillance

In an infected patient, point mutations at every position along the genome occur at least once every day



Pesistence of Latent Reservoirs



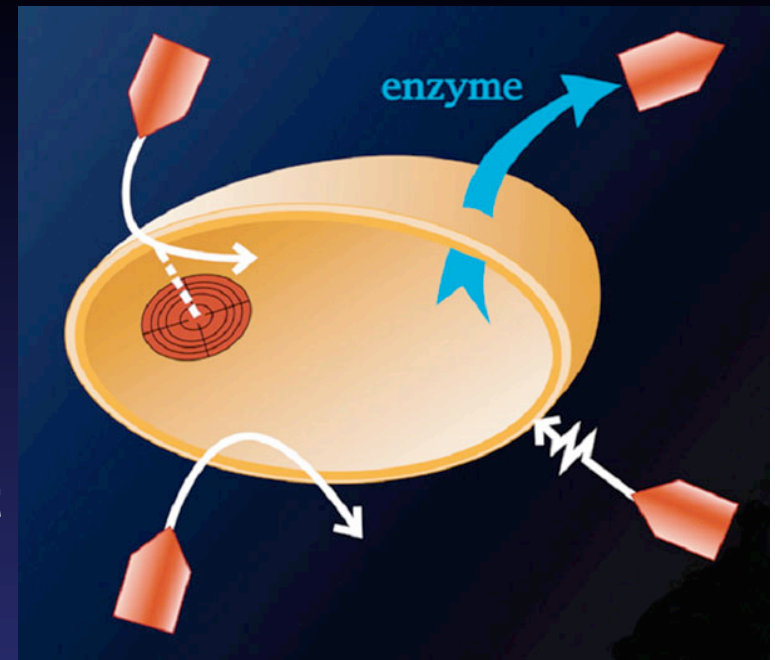
Drug Resistance

1. Resistance may be due to:

- i) prevention of penetration of the drug to its target site (lack of entry).
- ii) enzymatic destruction or inactivation of a drug.
- iii) cellular or metabolic changes at target site(s).
- iv) rapid efflux (pumping of drug out of cell) (greater exit).

2. Hereditary drug resistance, called resistance (R) factor.

Note: Resistance can be minimized by the discriminate use of drugs in appropriate concentrations and dosages.



Influenza Viruses

| | |
|--------|--------------------------------------|
| Type A | Potentially severe illness |
| | Epidemics and pandemics |
| | Rapidly changing |
| Type B | Usually less severe illness |
| | Epidemics |
| | More uniform |
| Type C | Usually mild or asymptomatic illness |
| | Minimal public health impact |

Centers for Disease Control (CDC) and Prevention. Influenza Prevention and Control. Influenza.
Available at: <http://www.cdc.gov/ncidod/diseases/flu/fluinfo.htm>.

Influenza Pandemics in the 20th Century

| Years | Flu Mortality | Virus | |
|-----------|---------------|---------------|----------------------|
| 1918-1919 | "Spanish" | Type A (H1N1) | 20 million worldwide |
| | | | 500,000 US |
| | "Asian" | Type A (H2N2) | 70,000 US |
| | "Hong Kong" | Type A (H3N2) | 34,000 US |

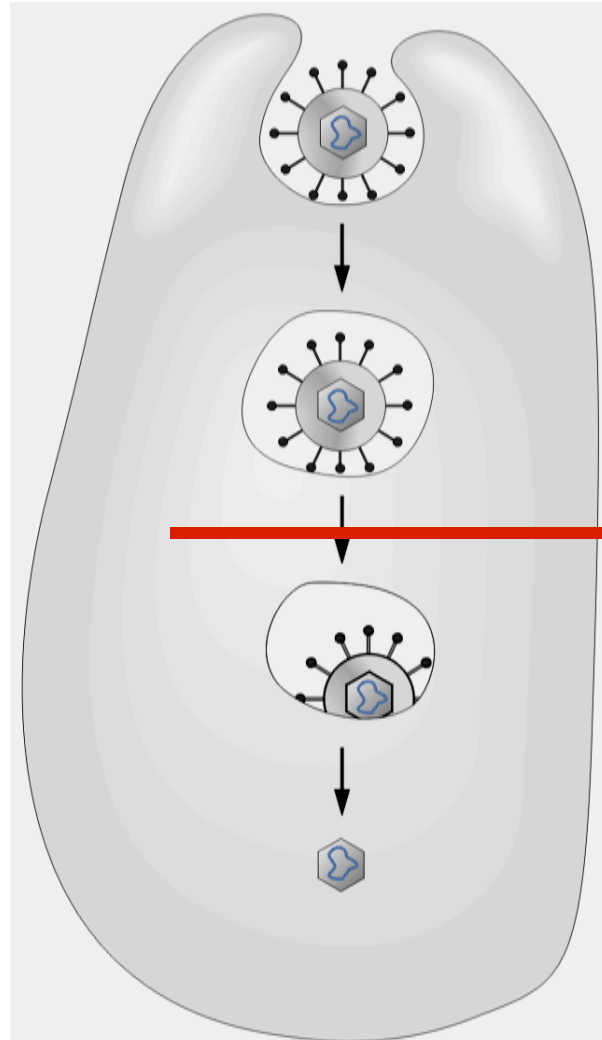
Glezen WP. *Epidemiol Rev.* 1996;18:65.

Centers for Disease Control and Prevention. Influenza Prevention and Control.

Influenza. Available at:

<http://www.cdc.gov/ncidod/diseases/flu/fluinfo.htm>.

Anti-influenza virus Agents



Block Uncoating
“A” specific
Amantadine/
Rimantidine

Amantadine (Symmetrel)

- A cyclic compound with an amino function group.

Mechanism of Action : Interferes with uncoating.

Pharmacokinetics : Orally administered with good absorption.

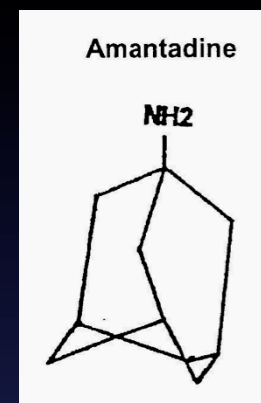
Therapeutics : Primarily used as a prophylactic drug for
Influenza-A virus.

--Recommended for use in high risk patients with cardiovascular, pulmonary, metabolic disorders.

Side effects/Toxicities:

- CNS toxicity : mostly excitability and insomnia.
- **Contraindicated in pregnancy due to teratogenic effects in animals.**

Note: Closely observe patients with history of epilepsy and reduce dosage in patients with renal function impairment



Amantadine (Cont.)

Drug Interactions:

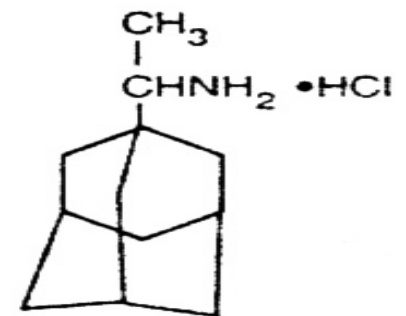
Anticholinergic drugs. Adjuvant therapy in Parkinson's disease patients.

Dyazides: hydrochlorothiazide and triamterene.

-- reduce the clearance of amantadine and can produce higher plasma concentrations and toxic effects.

Rimantadine (Flumadine) : A second generation Amantadine analog with similar mechanism of action.

- Preferred over Amantadine due to lower CNS toxicity and increased metabolism.



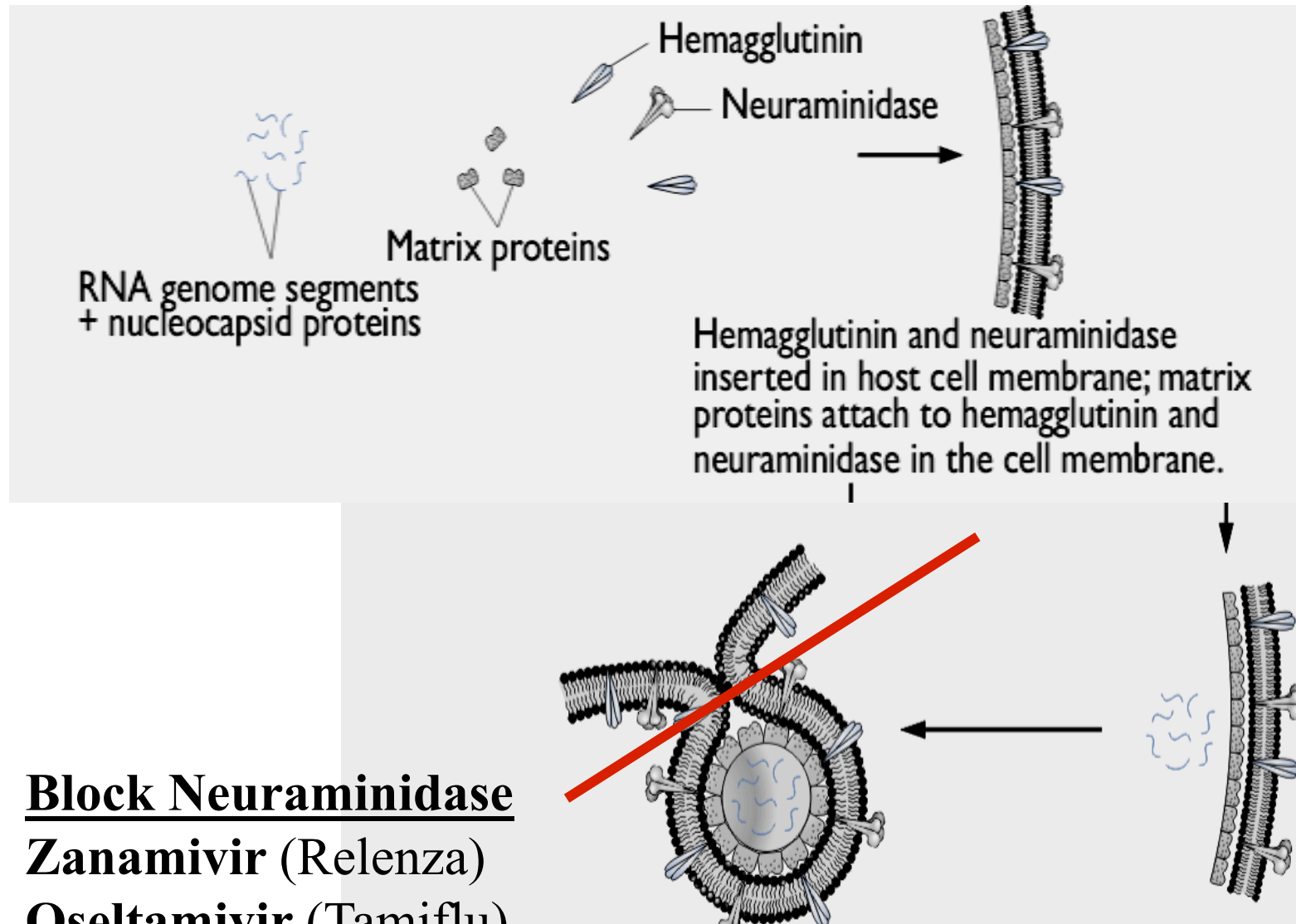
Rimantadine

Incidence of M2-Inhibitor Resistance among Human Influenza A (H3N2) Viruses in the United States.*

| Period | No. of Isolates Tested | No. That Showed Resistance (%) |
|-------------------------|-------------------------------|---------------------------------------|
| 1992–1995 | 991 | 8 (0.8) |
| 1996–1997 | 508 | 2 (0.4) |
| 1998–1999 | 510 | 11 (2.2) |
| 2000–2001 | 283 | 4 (1.4) |
| 2002 | 290 | 4 (1.4) |
| 2003 | 174 | 3 (1.7) |
| 2004 | 466 | 9 (1.9) |
| October 2004–March 2005 | 636 | 92 (14.5) |
| October–December 2005 | 209 | 193 (92.3) |

-- The CDC recently issued an **alert** instructing clinicians to avoid using M2 ion-channel inhibitors (amantadine and rimantadine) because Amantadine resistance has been detected at an extraordinarily high frequency in isolates of influenza A (H3N2) virus.

Alternative Drugs for Influenza virus infections:



Alternative Drugs for Influenza virus infections:

Zanamavir (Relenza)

Oseltamivir (Tamiflu) :

-- Influenza-A and -B.

-- Inhibits the viral neuraminidase enzyme required for cleavage of neuraminic acid and release of virus.

➤ Zanamivir is supplied as a topical formulation for inhalation.

➤ Oseltamivir is available in oral formulations.

-- TAMIFLU (Oseltamivir phosphate) : capsule (75 mg) or as powder for oral suspension.

Tamiflu™ (oseltamivir phosphate) – Types of Influenza Prophylaxis

- **Postexposure** – prophylaxis after exposure to influenza-infected individual(s) in household, workplace, social setting or community.
- **Seasonal** (during community outbreak) – prophylaxis for entire influenza season.
- **Postvaccination** – prophylaxis for 2-4 weeks after receiving influenza vaccine.
- **Outbreak control** – prophylaxis in institutional settings after influenza confirmed as present.

Tamiflu™ (oseltamivir phosphate)

Clinical Overview

- **Prevention of influenza in adults and adolescents ≥ 13 yrs**
- **Recommended dosage**
 - **75 mg qd $\times \geq 7$ days (PEP)**
 - **75 mg qd $\times 42$ days (seasonal)**
- **Safety and efficacy have been demonstrated for up to 6 weeks**
- **Tamiflu must be taken within 2 days of onset of symptoms.**

Herpes Viruses

- **Neurotropic virus** (HSV-1, HSV-2, VZV)
 - HSV-1: cold sores, genital herpes, encephalitis
 - HSV-2: genital herpes, neonatal herpes
 - VZV: varicella and zoster
- **Lymphotropic** (CMV, HHV-6, HHV-7, EBV, HHV-8)
 - **CMV**: mononucleosis, hepatitis, pneumonitis, retinitis, encephalitis
 - **HHV-6/7**: Encephalitis.
 - **HHV-8**: KS, Castleman's disease
 - **EBV**: mononucleosis, lymphoproliferative disease, BL, NPC

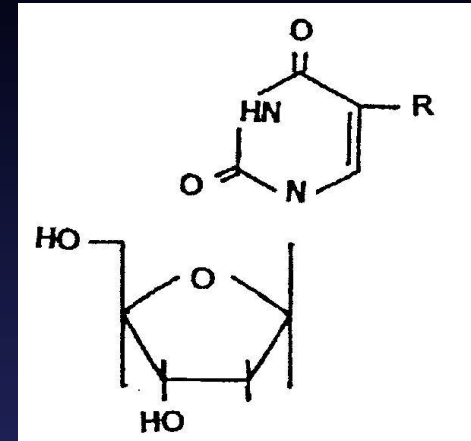
Properties of Herpes viruses

- All herpesviruses have the ability to establish latent infections.
- sequential expression of viral genes.
 - Immediate early, early and late phases.
- Complex genomes encoding many cellular homologues.
- Use rolling circle replication to produce new DNA.
- Many new antiviral targets have been identified through molecular and cell biological approaches.

Idoxuridine and Trifluridine

-- Thymidine analogs.

-CH₃ of thymidine is replaced by **-I** (Iodine) in Idoxuridine and by **-CF₃** in Trifluridine.



Mechanism of Action : inhibit DNA polymerase activity.

-- Activated intracellularly by host enzymes to the triphosphate form.

- Note: Can affect host DNA polymerases leading to bone marrow toxicity.

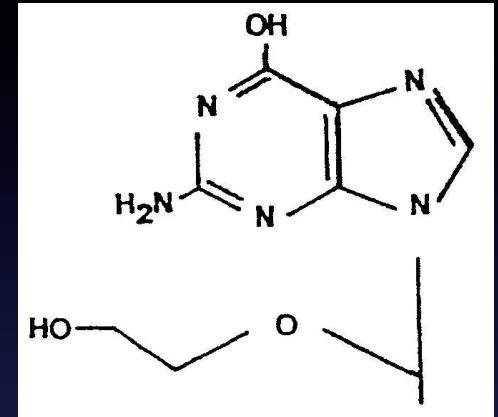
Therapeutics : used against Herpes Simplex Viruses (HSV).

-- Primarily indicated for treatment of Keratitis (in eye drops).

Side effects/Toxicities: Local hypersensitivity.

Acyclovir

- A Guanosine analog containing an acyclic side chain in place of ribose.



Mechanism of Action : Chain termination.

- Acyclovir is activated by the viral thymidine kinase (TK) enzyme to mono-phosphate.
- Host enzymes then convert the mono-phosphate to di- and tri-phosphates.
- The tri-phosphate analog then inhibits viral DNA polymerase activity by inhibiting DNA chain elongation due to lack of 3' –OH group.
- ❖ Viral Resistance can occur Due to mutations in viral TK enzyme.

Acyclovir (cont.)

Pharmacokinetics : Orally, intravenously or topically.

-- Only 50% of the plasma levels **penetrate the CSF**, hence dose escalation is required for the treatment of HSV encephalitis.

Therapeutics : Effective against HSV-2 (genital), HSV encephalitis and Varicella-Zoster.

➤ Not effective against CMV infections because CMV TK does not activate acyclovir.

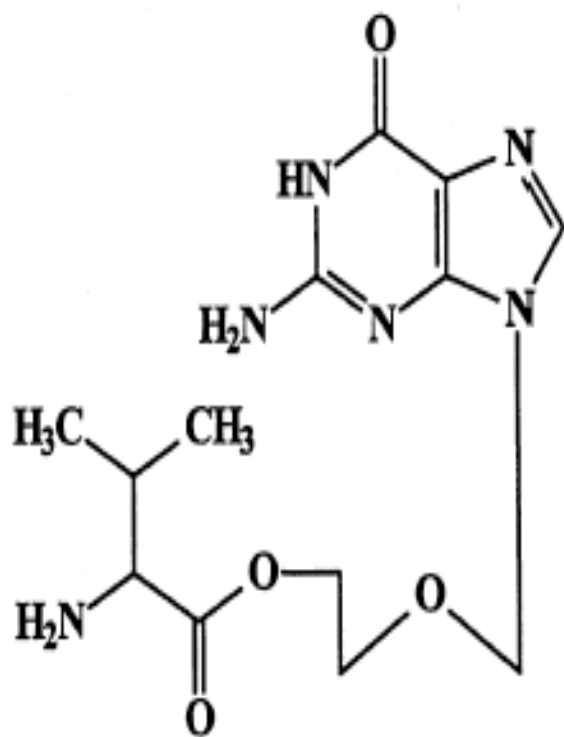
Side effects/Toxicities:

- Inflammation or phlebitis, malaise, nausea, diarrhea, and rash.
- Renal dysfunctions can occur with long term use.

Drug Interactions: Probenecid and Zidovudine.

Valaciclovir

➤ **Valine ester of acyclovir, acts as a prodrug.**



- Substantial increase in oral bioavailability over ACV.
- Allows drug levels to be achieved comparable to iv dosing.
- Clinical trials show activity against HSV-1,2 VZV, CMV.
- Reduction in patient pill burden

Valaciclovir

- **Valine ester of acyclovir, acts as a prodrug.**
- Stomach acids convert it to acyclovir.
- Achieves 3-5 fold higher plasma levels than acyclovir.
- Requires less frequent dosing.

Pharmacokinetics: Excretion in urine.

$T_{1/2} = 2.5 - 3 \text{ hrs.}$

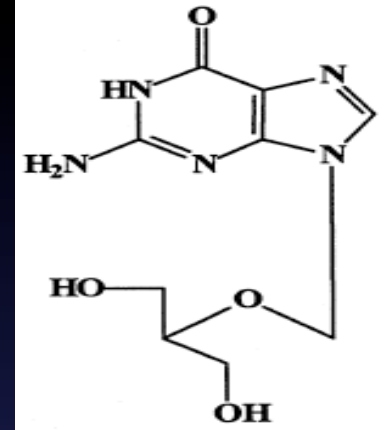
Therapeutics: Treatment of herpes zoster (shingles) and recurrent genital herpes.

Side effects: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS).

Drug Interactions: Cimetidine and probenecid.

Ganciclovir

- Structure similar to acyclovir except that it has an additional –CH₂OH group.



Mechanism : Activated by viral (HSV and CMV) thymidine kinase (TK) to mono-phosphate and then converted to di- and tri- phosphates by the host enzymes.

Pharmacokinetics : Not administered orally (only 6-7 % absorbed).

- Must be administered intravenously.
- Excreted 90% unchanged via the kidney.

Therapeutics : Primarily used against CMV infections.

Ganciclovir (cont.)

Side effects/Toxicities: **Bone marrow toxicity.**

- Causes significant **myelosuppression, neutropenia and thrombocytopenia.**
- May have CNS toxicity and may be toxic to the embryo (teratogenic).

Valganciclovir : A prodrug of Ganciclovir--
administered orally.

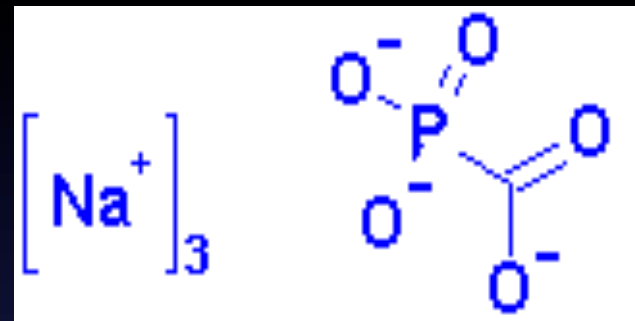
- For CMV retinitis in immunocompromised patients and transplant patients.

Drug Interactions: Imipenem-cilastin, nephrotoxic drugs, probenecid, didanosine, and zidovudine.

Note: May cause fatal dysfunctions such as **pancreatitis, sepsis and multiple organ failure.**

Foscarnet

A tri-sodium salt of phosphonoformate.



Mechanism of Action : Inhibits viral DNA polymerase.

- Competes for pyrophosphate binding site on DNA Polymerase.

Pharmacokinetics : Poorly absorbed orally, given I.V.

Therapeutics : Effective against acyclovir-resistant HSV.

- Also indicated as an alternative drug against CMV infections.

Side effects/Toxicities : Mostly associated with cation problems such as hypokalemia and hypomagnesemia.

Drug Interactions: Nephrotoxic drugs (e.g. aminoglycoside, amphotericin B, pentamidine).

Novel Anti-HSV Agents: Promising times?

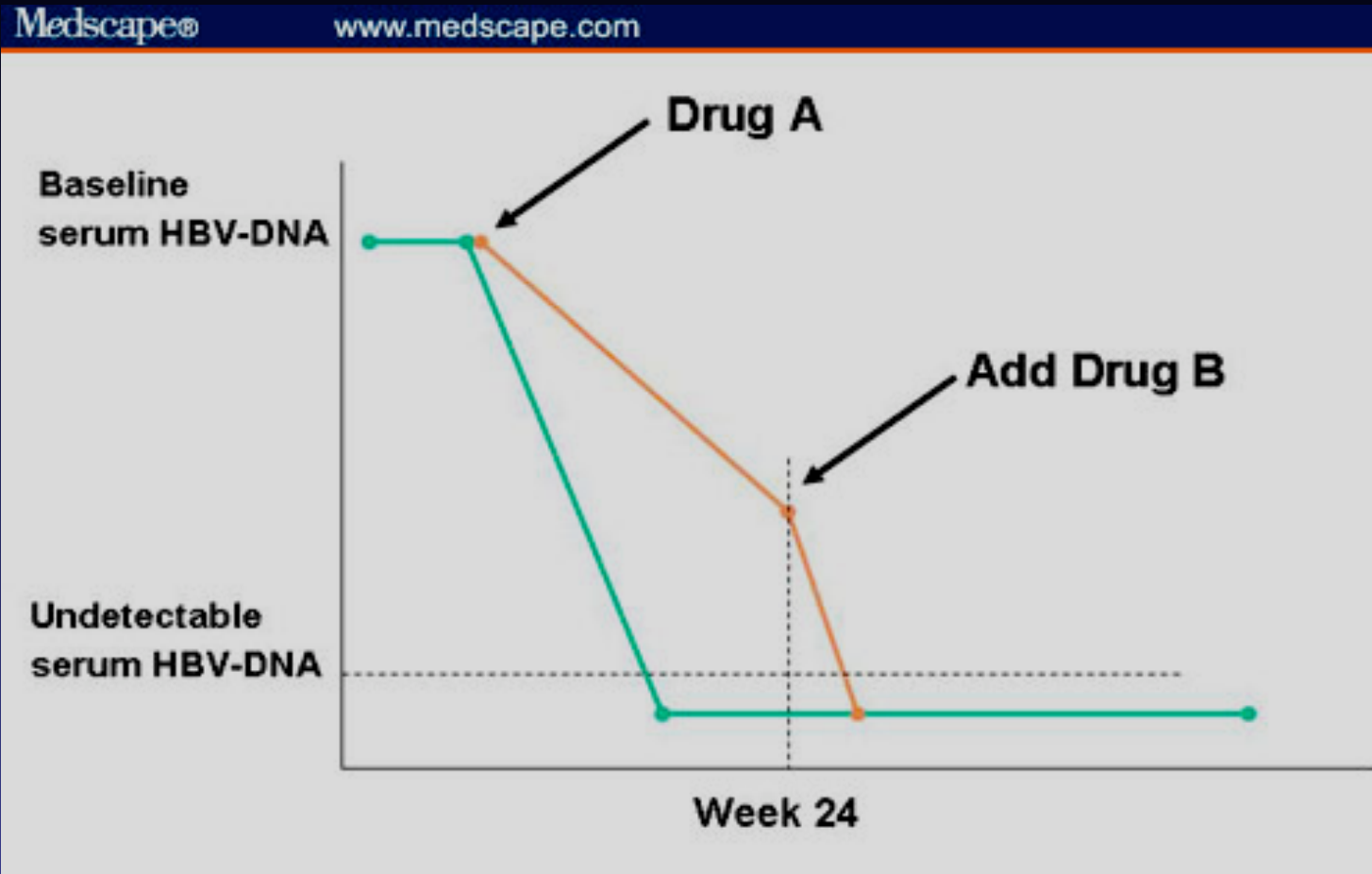
- Significant improvements in bioavailability of established anti-herpetics has occurred.
- A number of anti-herpetics are undergoing early evaluation which target novel processes such as:
 - DNA replication/ maturation (GW-275175X, BAY-38-4766; PNU-183792)
 - Helicase primase action (BAY-57-1293; BILS 179BS)
 - Protein kinase functions (maribavir)
 - Protein-protein interactions (BILD 1263)

Hepatitis Viruses



| Virus Family | Hepatitis A Picornavirus | Hepatitis E Calicivirus | Hepatitis B Hepadnavirus | Hepatitis C Flavivirus | Delta virus Satellite virus (only in combination with HBV) |
|-------------------------|--|----------------------------|---|--|--|
| Commonality | All generate conditions of illness in the liver | | | | |
| Symptoms (acute) | All the same – malaise, dark urine, anorexia, nausea, vomiting, jaundice | | | | |
| Transmission | Enteric (food and water) | | Sex, blood and close contact | | |
| Chronic condition | No | No | Yes | Yes | Yes |
| Virus genome | +ss RNA | +ss RNA | DNA with reverse transcriptase activity | +ss RNA | -ss RNA |
| Virus antigens | HA Ag | HEV ORF2 proteins | HBsAg HBcAg HBeAg | Many – core E1 E2 NS3 | Delta antigen |
| Incubation | 1 month (15 – 50 d) | | 4 months (45 – 160 d) | 2 months (15 – 150 d) | 1 – 2 months |
| Current therapeutics | No specific treatment | No specific treatment | Interferon alpha, Lamivudine, Adefovir, Etecovir | Interferon alpha + ribavirin, Pegylated Interferon | Follow HBV therapy |
| Vaccines available? | Yes Havrix (GSK) Vacta (Merck) | No | Yes Engerix-B (rHBsAg) GSK Recombivax B (Merck) | No | Can be prevented by vaccination against HBV |

Treatment approach for HBV



Beginning with a drug (A) having a high genetic barrier. If the viral load remains detectable at Week 24, another compound (B) with minimal cross-resistance should be added.

Interferon- α

- A polypeptide cytokine (mw. 18,000-20,000).
- INF- α from leukocytes, INF- β from fibroblasts, INF- γ from T-cells.
- Generated by recombinant DNA techniques.

Mechanism of Action :

- * Activates ribonucleases which degrade viral mRNA.
- Blocks protein synthesis by inhibiting translation initiation complex.

Therapeutics : Broad spectrum activity, inhibits both DNA and RNA viruses. However, primarily indicated against Hepatitis-B and -C infections.

- Administered intramuscularly or subcutaneously.

Interferon α (cont.)

Side effects/Toxicities:

- Causes flu like symptoms.
- High doses can cause bone marrow suppression.
- Photosensitivity may also occur.

Drug Interactions: Aminophylline and Zidovudine.

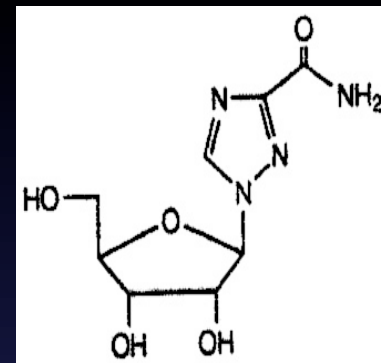
- Standard hematologic tests should be performed.

PEG-Interferon α :

- Pegylated interferons have a longer half-life, require fewer doses and are more effective.
- Highly efficacious against HBV and HCV when administered in combination with ribavirin.

Ribavirin

A synthetic triazine riboside analog.



Mechanism : A two-prong effect.

- Converted intracellularly to 5'-triphosphate derivative which inhibits viral RNA polymerase.
- Also inhibits capping of viral mRNA at the 5' position.

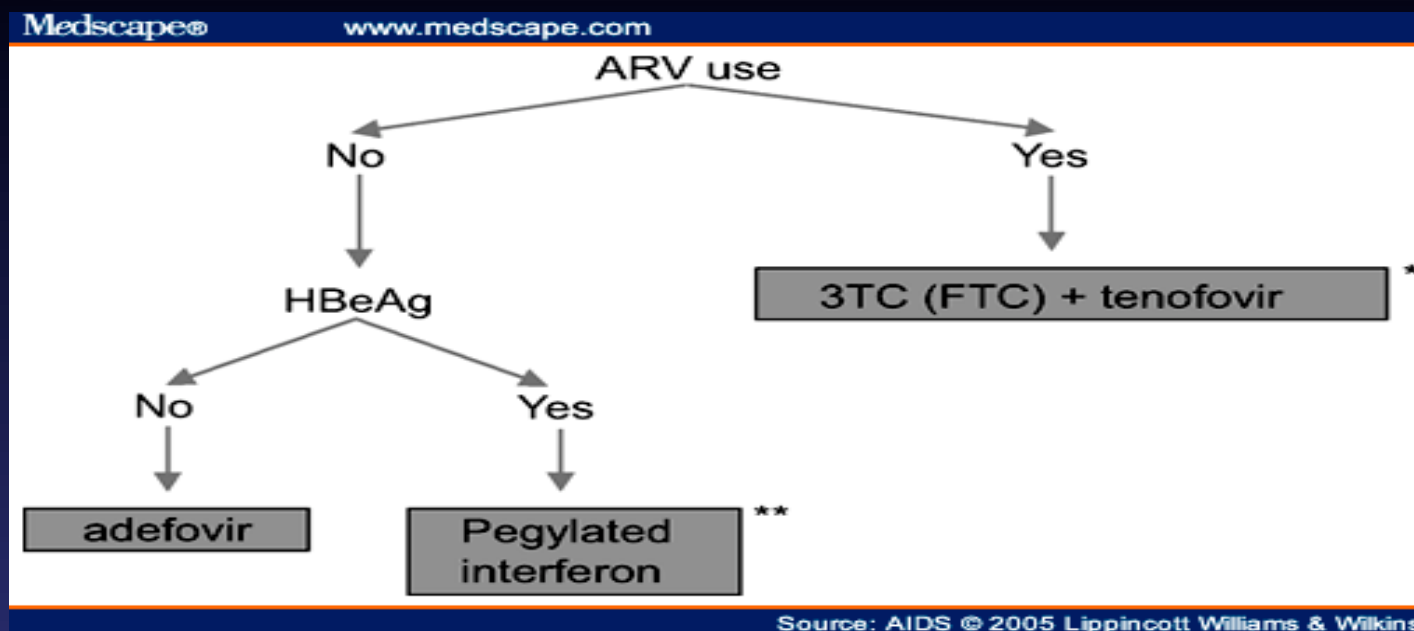
Pharmacokinetics : Administered both orally and I.V.

Therapeutics : Primarily used against **Respiratory Syncytial Virus (RSV) infections**, usually as an aerosol.

-- used In combination with **Interferon α -2b** for HCV infections.

Side effects/Toxicities: Causes anemia, elevates bilirubin and may also have teratogenic effects.

HBV and HIV-1 co-infected patients.



ARV, Antiretroviral drug; FTC, emtricitabine; 3TC, lamivudine.

-- Several anti-HIV drugs are used nowadays in HIV-1/HBV coinfecting patients.

Lamivudine (3TC), a nucleoside analog anti-HIV-1 drug, is used in combination with Interferon a-2b for treatment of HBV infection.

Tenofovir (Viread). A nucleotide reverse transcriptase inhibitor prescribed for both hepatitis B and HIV.

| Virus | Drug of Choice | Alternate |
|--|---|-----------------------|
| Influenza-A | Amantadine, Rimantadine | No alternative |
| Influenza A and B | Zanamivir, Oseltamivir | |
| Herpes simplex (keratitis) | Trifluridine (topical) | Idoxuridine (topical) |
| Herpes simplex (encephalitis) | Acyclovir | Foscarnet |
| CMV | Ganciclovir, Valganciclovir | Foscarnet |
| Herpes simplex (genital) | Acyclovir, Valacyclovir | |
| Herpes simplex (Acyclovir-resistant) | Foscarnet | |
| Respiratory Syncytial Virus (RSV) | Ribavirin | |
| Varicella-Zoster | Acyclovir, Valacyclovir | Foscarnet |
| Hepatitis-B (chronic) | IgG, Lamivudine, Interferon α | |
| Hepatitis A,B and C. (HIV-coinfection) | INF α /PEG-INF α + ribavarin (ARV+Lamvudine/Adefovir) | |